

techniques are described in the literature [see, for example, Klein et al., *Proc. Natl. Acad. Sci.*, **93**:7108-7113 (1996); U.S. Patent No. 5,536,637]. The results of such efforts are provided herein.

#### 57. PRO704

VIP36 is localized to the Golgi apparatus and the cell surface, and belongs to a family of legume lectin homologues in the animal secretory pathway that might be involved in the trafficking of glycoproteins, glycolipids, or both. It is further believed that VIP36 binds to sugar residues of glycosphingolipids and/or glycosylphosphatidylinositol anchors and might provide a link between the extracellular/luminal face of glycolipid rafts and the cytoplasmic protein segregation machinery. Further regarding VIP36, it is believed that there is a signal at its C-terminus that matches an internalization consensus sequence which confers its ability to cycle between the plasma membrane and Golgi. See, Fiedler, et al, *EMBO J.*, 13(7):1729-1740 (1994); Fiedler and Simons, *J. Cell Sci.*, 109(1):271-276 (1996); Itin, et al., *MBO J.*, 14(10):2250-2256 (1995). It is believed that VIP36 is either the same as or very closely related to the human GP36b protein. VIP36 and/or GP36b are of interest.

More generally, vesicular, cytoplasmic, extracellular and membrane-bound proteins play important roles in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. These secreted polypeptides or signaling molecules normally pass through the cellular secretory pathway to reach their site of action in the extracellular environment, usually at a membrane-bound receptor protein.

Secreted proteins have various industrial applications, including use as pharmaceuticals, diagnostics, biosensors and bioreactors. In fact, most protein drugs available at present, such as thrombolytic agents, interferons, interleukins, erythropoietins, colony stimulating factors, and various other cytokines, are secretory proteins. Their receptors, which are membrane-bound proteins, also have potential as therapeutic or diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents to block receptor-ligand interaction. Membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor kinases, receptor phosphatases, receptors involved in cell-cell interactions, and cellular adhesion molecules like selectins and integrins. Transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and nerve growth factor receptor.

Efforts are being undertaken by both industry and academia to identify new, native vesicular, cytoplasmic, secreted and membrane-bound receptor proteins, particularly those having sequence identity and/or similarity with VIP36. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted and membrane-bound receptor proteins. Examples of

screening methods and techniques are described in the literature [see, for example, Klein et al., Proc. Natl. Acad. Sci., 93:7108-7113 (1996); U.S. Patent No. 5,536,637].

**58. PRO706**

Acid phosphatase proteins are secreted proteins which dephosphorylate terminal phosphate groups under acidic pH conditions. Acid phosphatases contain a RHGXRX amino acid sequence, which is predicted to be mechanistically significant. Acid phosphatases may have important functions in the diagnosis and treatment of human diseases. For example, prostatic acid phosphatase is a secreted protein uniquely expressed in prostatic tissue and prostate cancer. The level of prostatic acid phosphatase is a potential prognostic factor for local and biochemical control in prostate cancer patients treated with radiotherapy, as described in Lankford et al., Int. J. Radiat. Oncol. Biol. Phys., 38(2): 327-333 (1997). Research suggests that a cellular immune response to prostatic acid phosphatase may mediate destructive autoimmune prostatitis, and that xenogeneic forms of prostatic acid phosphatase may prove useful for immunotherapy of prostate cancer. See Fong et al., J. Immunol., 169(7): 3113-3117 (1997). Seminal prostatic acid phosphatase levels correlate significantly with very low sperm levels (oligospermia) in individuals over 35, see Singh et al., Singapore Med. J., 37(6): 598-599 (1996). Thus, prostatic acid phosphatase has been implicated in a variety of human diseases, and may have an important function in diagnosis and therapy of these diseases. A series of aminobenzyolphosphoric acid compounds are highly potent inhibitors of prostatic acid phosphatase, as described in Beers et al., Bioorg. Med. Chem., 4(10): 1693-1701 (1996).

More generally, extracellular proteins play an important role in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. These secreted polypeptides or signaling molecules normally pass through the cellular secretory pathway to reach their site of action in the extracellular environment.

Secreted proteins have various industrial applications, including pharmaceuticals, diagnostics, biosensors and bioreactors. Most protein drugs available at present, such as thrombolytic agents, interferons, interleukins, erythropoietins, colony stimulating factors, and various other cytokines, are secretory proteins. Their receptors, which are membrane proteins, also have potential as therapeutic or diagnostic agents. Efforts are being undertaken by both industry and academia to identify new, native secreted proteins, particularly those having sequence identity with prostate acid phosphatase precursor and lysosomal acid phosphatase precursor and in some cases, those having identity with DNA found in fetal heart. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., Proc. Natl. Acad. Sci., 93:7108-7113 (1996); U.S. Patent No. 5,536,637].

**59. PRO707**

Cadherins are a large family of transmembrane proteins. At least cadherins 1-13 as well as types B, E, EP, M, N, P and R have been characterized. Among the functions cadherins are known for, with some exceptions, cadherins participate in cell aggregation and are associated with cell-cell adhesion sites. Cadherins are further described in Tanihara, et al., J. Cell Sci., 107(6):1697-1704 (1994) and Tanihara, et al., Cell Adhes. Commun., 2(1):15-26 (1994). Moreover, it has been reported that some members of the cadherin superfamily are involved in general cell-cell interaction processes including transduction. See, Suzuki, J. Cell Biochem., 61(4):531-542 (1996). Therefore, novel members of the cadherin superfamily are of interest.

More generally, all novel proteins are of interest, including membrane-bound proteins. Membrane-bound proteins and receptors can play an important role in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor kinases, receptor phosphatases, receptors involved in cell-cell interactions, and cellular adhesion molecules like selectins and integrins. For instance, transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and nerve growth factor receptor.

Membrane-bound proteins and receptor molecules have various industrial applications, including as pharmaceutical and diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents to block receptor-ligand interaction. The membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction.

Efforts are being undertaken by both industry and academia to identify new, native secreted and membrane-bound receptor proteins, particularly membrane bound proteins having identity with cadherins. The results of such efforts are provided herein.

#### 60. PRO322

Proteases are enzymatic proteins which are involved in a large number of very important biological processes in mammalian and non-mammalian organisms. Numerous different protease enzymes from a variety of different mammalian and non-mammalian organisms have been both identified and characterized, including the serine proteases which exhibit specific activity toward various serine-containing proteins. The mammalian protease enzymes play important roles in biological processes such as, for example, protein digestion, activation, inactivation, or modulation of peptide hormone activity, and alteration of the physical properties of proteins and enzymes.

Neuropsin is a novel serine protease whose mRNA is expressed in the central nervous system. Mouse neuropsin has been cloned, and studies have shown that it is involved in the hippocampal plasticity. Neuropsin has also been indicated as associated with extracellular matrix modifications and cell migrations. See, generally,